

Applicants: Anna Marie Pyle and Eckhard Jankowsky
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distinguishing Figure 4A and 4B is missing.

(c) The Examiner stated that in Figure 6, a label distinguishing Figure 6A, 6B and 6C is missing.

(d) The Examiner stated that Figure 9 is unlabeled.

The Examiner stated that correction is required.

In response, applicants first maintain that Figure 9 is not unlabeled. Applicants direct Examiner's attention to the top center of Drawing page 10/14 which indicates that the figure on the page is indeed labeled as "Figure 9". Regarding the remaining corrections proposed by the Examiner, applicants submit herewith, as Exhibit A, a Letter With Proposed Drawing Changes, including print sketches with such corrections shown in red ink. In addition, applicants have provided Drawing page numbers for each of the Drawing Pages. Applicants will submit formal Drawings upon the indication of allowable subject matter.

Objection to specification

The Examiner objected to the specification because of the following informalities:

(a) The Examiner stated that the word "Breif" in the "Brief Description of the Figures" at page 5, line 1 is misspelled.

The Examiner suggested changing "Breif" to "Brief".

The Examiner stated that appropriate correction is required.

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In response, applicants have amended the specification at page 5, line 1 to correct the obvious typographical error in the spelling of the word "Brief". Applicants believe that the amendment to the specification obviates the Examiner's objection.

The Examiner stated that the numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. The Examiner stated that when claims are canceled, the remaining claims must not be renumbered. The Examiner stated that when new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

The Examiner stated that misnumbered claims 4-6 at page 44 of the specification have been renumbered as claims 1-3.

In response, applicants acknowledge Examiner's renumbering of the claims.

Claim Rejections-35 USC § 112, second paragraph

The Examiner rejected claims 1-8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that claims 1-6 are indefinite for reciting "being capable of" in claim 1, step (a) because it cannot be determined whether "capable of" is a property of the first label or a method step. The Examiner suggested deleting "being capable

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of".

In response, without conceding the correctness of the Examiner's position, and to expedite prosecution of the subject application, applicants have amended claim 1 to recite in step a) ". . . a first RNA having a first label attached thereto and a second RNA, wherein said first label produces a luminescent energy pattern when the first RNA is present in the RNA duplex, which luminescent energy pattern differs from the luminescent energy pattern produced when the first RNA is not present in the RNA duplex." Applicants maintain that claim 1 as amended is not indefinite and does in fact particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants maintain, therefore, that the amendment to claim 1 obviates the above ground of Examiner's rejection.

The Examiner stated that claims 1-6 are confusing in claim 1 at step (b) because step (b) appears to be redundant to step (a) and it cannot be determined how the method steps differ. The Examiner stated that clarification is required.

In response, without conceding the correctness of Examiner's position, but to expedite prosecution of the subject application, applicants have amended claim 1 for clarification by deleting previous step b). Applicants maintain that the amendment to claim 1 obviates the above ground of Examiner's rejection.

The Examiner stated that claims 1-3 are confusing at "first label" because it appears that multiple labels are used in the method, but only one label is disclosed. The Examiner suggested inserting after "a second RNA" in claim 1, step (a), "having a

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second label attached thereto" as suggested in the specification at page 14.

In response, applicants respectfully traverse the Examiner's rejection of claims 1-3. Applicants maintain that claim 1 is clear as written. Reference to a first label in claim 1 without reference to additional labels does not create an appearance, as Examiner suggests, that multiple labels are used in the method. The Examiner suggests adding words to claim 1 which would introduce a limitation not present or intended to be present in the claim. Applicants point out to the Examiner that claims 4-6, which depend from claim 1, recite a second label that is distinct from the first label recited in claim 1. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-3.

The Examiner rejected claims 1-6 as being incomplete for omitting an essential element in claim 1, such omission amounting to a gap between the elements. The Examiner directed applicants to see MPEP § 2172.01. The Examiner stated that the omitted element is a step in claim 1 wherein ATP and a divalent cation are required for RNA helicase to unwind the RNA duplex as recited in the specification at page 38, subheading "Helicase Reaction". The Examiner stated that, additionally, Shuman also teaches that ATP and a divalent cation are required for helicase activity (10936, lines 40-52). The Examiner, therefore, suggested combining claims 1 and 2.

In response, applicants respectfully traverse the Examiner's rejection of claims 1-6. Applicants maintain that claim 1 contains no omission of an essential element and that there is

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no gap between the elements in the claim. Claim 1 recites at step a) "admixing an RNA helicase with the RNA duplex under conditions permitting the RNA helicase to unwind the RNA duplex and release single-stranded RNA, wherein the RNA duplex comprises a first RNA having a first label attached thereto and a second RNA, wherein said first label produces a luminescent energy pattern when the first RNA is present in the RNA duplex, which luminescent energy pattern differs from the luminescent energy pattern produced when the first RNA is not present in the RNA duplex." Applicants direct Examiner's attention to the specification at page 14, lines 21-25, which states that "conditions which permit the RNA helicase to unwind the RNA duplex and release single-stranded RNA preferably include, but are not limited to the presence of ATP and a divalent cation." It is clear, therefore, that by including in claim 1 the element of "conditions permitting the RNA helicase to unwind the RNA duplex and release single-stranded RNA, wherein the RNA duplex comprises a first RNA having a first label attached thereto and a second RNA, wherein said first label produces a luminescent energy pattern when the first RNA is present in the RNA duplex, which luminescent energy pattern differs from the luminescent energy pattern produced when the first RNA is not present in the RNA duplex" and providing in the specification a clear description of such conditions, applicants have not omitted an essential element in claim 1 as Examiner suggests. Applicants, therefore, respectfully request that Examiner reconsider and withdraw the above rejection of claims 1-6.

In view of the amendments and arguments presented hereinabove, applicants maintain that claims 1-8 are not indefinite and do not fail to particularly point out and distinctly claim the subject

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matter which applicants regard as their invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-8 under 35 U.S.C. 112, second paragraph.

Claim Rejections under 35 USC § 103(a)

The Examiner rejected claims 1-8 under 35 U.S.C. 103(a) as being unpatentable over Shuman (Proc. Natl. Acad. Sci. USA, November 1992), in view of Bjornson et al. (Biochemistry, December 1994). The Examiner stated that regarding claim 1, Shuman discloses a method for detecting the release of a single-stranded RNA from an RNA duplex which comprise (a) admixing an RNA helicase with the RNA duplex under conditions permitting the RNA duplex to unwind the RNA duplex and release single stranded RNA, wherein the RNA duplex comprises a first RNA having a label and a second RNA wherein the unwound single-stranded RNA released from the duplex is detected by gel electrophoresis (page 10936 col. 1, lines 18-29 and 40-52, see Figure 1 and Figure 2). The Examiner stated that the method of Shuman differs from that of the claimed invention in that Shuman does not teach wherein the first label is capable of producing a luminescent energy pattern when the first RNA is present in the RNA duplex which differs from the luminescent pattern produced when the first RNA is not present in the RNA duplex.

The Examiner stated that the reference also does not teach detecting a change in the luminescent energy pattern produced by the first label to thereby detect release of a single-stranded RNA from the RNA duplex. The Examiner stated that Bjornson et al. (Biochemistry, December 1994) teach a method for detecting the release of a single stranded DNA molecule from a DNA duplex

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comprising admixing a helicase with a DNA duplex under conditions permitting the helicase to unwind the duplex and release single stranded DNA, wherein the first strand of the DNA substrate I has a label attached thereto at the 3' end and the second strand of the DNA substrate I has a label attached thereto at its 5' end, wherein the first label is capable of producing a luminescent energy pattern, detecting changes in the luminescent energy pattern produced by the first label so as to thereby detecting release of single-stranded DNA from the DNA duplex (page 14309, last paragraph col. 1 to first paragraph col. 2, see also page 14310, Figure 2). The Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Shuman with the teaching of Bjornson et al. to obtain the claimed invention because the skilled artisan would have been motivated to improve the method of Shuman by incorporating a label useful in a fluorescence based assay to detect the release of single stranded RNA from the RNA duplex with a reasonable expectation of success by the teaching of Bjornson et al. that a fluorescent based assay has several obvious advantages for kinetic studies in general and particularly for mechanistic studies for helicase-catalyzed unwinding. The Examiner stated that, first, such an assay is extremely sensitive (Abstract), allowing unwinding to be monitored continuously in real time. The Examiner stated that second, a full kinetic time course can be obtained from a single experiment with more accurate determination of the observed kinetic parameters, and third the data can be easily imported into numerical simulation programs choice of a first and second label would have been determined by the skilled artisan based on commercial availability, experimental procedures and desired results.

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The Examiner stated that, regarding claim 7, Bjornson et al. disclose a method of measuring the rate of release of DNA from a DNA duplex which comprise detecting whether single stranded DNA is released from the duplex at predetermined time intervals and determining the rate of release of the single stranded DNA from the duplex (page 14310, Figure 2 and col. 2, first and second full paragraphs).

The Examiner stated that regarding claim 8, Shuman discloses a method of determining whether a compound is capable of modulating the release of a single stranded RNA from an RNA duplex by an RNA helicase which comprises detecting the release of the single stranded RNA from the RNA duplex, wherein the compound (AMPPNP or AMPPCP) is added to the mixture comprising the RNA helicase, RNA duplex and label (page 10937, figure 5)

In response, applicants respectfully traverse the Examiner's rejection of claims 1-8 under 35 U.S.C. 103(a) as being unpatentable over Shuman (Proc. Natl. Acad. Sci. USA, November 1992), in view of Bjornson et al. (Biochemistry, December 1994). Applicants' claimed invention is directed to, *inter alia*, a method for detecting the release of a single-stranded RNA from an RNA duplex which comprises: a) admixing an RNA helicase with the RNA duplex under conditions permitting the RNA helicase to unwind the RNA duplex and release single-stranded RNA, wherein the RNA duplex comprises a first RNA having a first label attached thereto and a second RNA, wherein said first label produces a luminescent energy pattern when the first RNA is present in the RNA duplex, which luminescent energy pattern differs from a luminescent energy pattern produced when the first RNA is not present in the RNA duplex; and b) detecting a change

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in the luminescent energy pattern produced by the first label so as to thereby detect release of single-stranded RNA from the RNA duplex.

Shuman teaches a method of detection by gel electrophoresis of RNA unwinding which uses a radiolabel attached to an RNA strand. Examiner correctly acknowledges that in contrast to applicants' claimed invention, Shuman does not teach the use of a label which produces a luminescent energy pattern. Bjornson, et al. teaches a method for detecting the release of a single stranded DNA molecule from a DNA duplex. The Examiner takes the position that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teaching of Shuman with the teaching of Bjornson and obtain the applicants' claimed invention. The Examiner appears to have applied an "obvious to try" standard in the present case. The standard for determining obviousness is whether one of ordinary skill in the art would have a reasonable expectation of success in carrying out the claimed invention in view of the cited references. Clearly, it is well settled law that the "obvious to try" standard is not the standard to be applied in an obviousness analysis. See M.P.E.P. §2145. One with ordinary skill in the art will readily recognize that the combination of the Shuman and Bjornson references does not render obvious applicants' claimed invention. An ordinarily skilled artisan would recognize that there would be no reasonable expectation of success in a method of detecting RNA unwinding using a label which produces a luminescent energy pattern based on the teaching of a method using a radiolabel attached to an RNA strand in combination with the teaching of a label capable of producing a luminescent energy pattern when attached to a DNA strand. One with skill in the art

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will recognize that RNA presents obstacles to success that are not present with DNA and for which the applicants' claimed invention provides a solution. Specifically, one with skill in the art would recognize that applicants' claimed invention overcomes the difficulty that exists in making an RNA strand and attaching a luminescent dye to it--difficulties that are not present with DNA. The cited references, either alone or in combination, even if motivating one to try the applicants' claimed invention (although applicants do not concede that such a motivation exists in the present case) would not present a reasonable expectation of success in doing so. Accordingly, applicants maintain that the Shuman and Bjornson references do not render obvious the applicants' claimed invention, and respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-8 under 35 U.S.C. 103(a).

Additional Prior Art cited by the Examiner

The Examiner stated that the prior art made of record is considered pertinent to applicant's disclosure. The Examiner stated that Kowalczykowski et al. (5,747,247 May 5, 1998) disclose a method for detecting helicase activity and inhibition using luminescent markers (labels).

Applicants note that Examiner has not issued a rejection based on the Kowalczykowski et al. (5,747,247 May 5, 1998) reference.

Examiner's Conclusion

The Examiner stated that no claims are allowed.

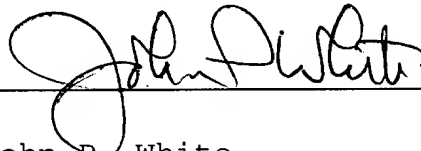
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned

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attorney invites the Examiner to telephone him at the number provided below.

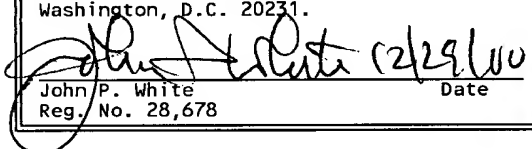
No fee, other than the enclosed \$445.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. If any other fee is required, however, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.


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Date